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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SOUAYA, JEHANNE E	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,196	WANG ET AL.	
	Examiner	Art Unit	
	Jehanne E Souaya	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *25 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *2 and 8-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7/2001* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *1449: 8/2002; 9/2002* .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group 1, claims 1, 5-7 is acknowledged. The traversal is on the ground(s) that claims 3 and 4 should be added. This argument was found persuasive, and therefore, claims 1, and 3-7 will be examined. Further, claim 16 was erroneously excluded but was intended to be added to group XI. With regard to claim 12, such was erroneously included in group IV, but should be in group V, as indicated. Claim 13 was erroneously placed in group IV and should be included in Group II. Claim 14 was erroneously placed in group IV and should be included in group X. Group IV, drawn to a method of detecting polynucleotides was intended to contain claim 3-4, however, the restriction requirement between groups I and IV is withdrawn and claims 1 and 3-7 will be examiner. Further, SEQ ID NOS 1, 3, and 5 will also be examined together, and the requirement to elect a single sequence is withdrawn. The response does not traverse the remainder of the restriction requirement which is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1 and 3-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described

in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to nucleic acids that consist essentially of (considered open terminology and interpreted like "comprising") a nucleotide sequence "according to SEQ ID NOS 1, 3, and 5", sequences having at least 85% identity to the nucleotide sequence according to SEQ ID NOS 1, 3, and 5, complements of SEQ ID NOS 1, 3, and 5, and sequences that hybridize to a sequence according to SEQ ID NOS 1, 3, and 5. Such recitation encompasses mutants, variants, and homologs of SEQ ID NOS 1, 3, and 5, from any source. However, the specification does not provide enough guidance to the skilled artisan to make or use sequences commensurate in scope with the broadly claimed invention.

The specification teaches that SEQ ID NO 5 encodes a matrix metalloprotease that has the highest % identity to the stromelysin family of matrix metalloproteases (46%). The specification teaches that SEQ ID NO 3 encodes a splice variant of SEQ ID NO 5,which lacks a Zn binding domain. The specification teaches that SEQ ID NO 1 encodes a fragment of SEQ ID NO 5, and SEQ ID NO 3. The specification teaches that the claims encompass variants that retain structural and functional characteristics more similar to MMP 25 (polypeptide encoded by SEQ ID NO 5) than to non type MMP 25 polypeptides. However, the specification does not teach the specific biological activity or function of SEQ ID NOS 3 or 5, such that the skilled artisan could predictably determine whether a nucleic acid encoded a matrix metalloprotease or MMP 25, based solely on it's nucleic acid sequence or it's ability to hybridize to any of SEQ ID NO 1, 3, or 5.

While SEQ ID NO 5 appears to belong to the family of Matrix Metalloproteases, Matrix Metalloproteases comprise a large group of proteins that are involved in the degradation of the extracellular matrix (see Yang and Kurkinen, J. BC, 1998; vol. 273, p 17893, col 1). This large group of proteins share similar domains with distinct structure and function, and have wide and often overlapping substrate specificities depending on the group they are in. These groups include collagenases, gelatinases, stromelysins, and membrane-type MMPs. However, this large group of proteins have different biological functions. Nagase teaches (Nagase and Woessner, J. BC, vol. 274, pp 21491-21494; 1999) that MMPs participate in many normal biological processes such as embryonic development, organ morphogenesis, nerve growth, apoptosis, etc (see p. 21493, col. 1 "Biological and Pathological Roles of Matrixins"). Nagase teaches that while the main function of matrixins is removal of the extracellular matrix during tissue resorption and progression of many diseases, MMPs also alter biological functions of extracellular matrix macromolecules by specific proteolysis. Nagase teaches that MMP-2 cleaves the Ala586-Leu587 bond in laminin and induces the migration of normal breast epithelial cells. In contrast, cleavage of type I collagen by MMP-1 and MMP-13 initiates keratinocyte migration during reepithelialization and osteoclast activation. Fig 1 of Nagase illustrates the structural similarities and differences between known matrix metalloproteases. Further, the degree of % identity of SEQ ID NO 5 to stromelysins does not indicate a particular biological function or activity for SEQ ID NOS 1, 3, or 5, or functional fragments of such, as the art teaches that stromelysins do not necessarily have the same activity. For example, Luo et al (JBC, vol. 277, pp 25527-25536, 2002) teaches that unlike most MMPs, ST3 (MMP 11) is characterized by a distinct substrate specificity and a specific regulation and is not directly involved in

extracellular matrix degradation (see abstract). Bodey et al (In Vivo, vol. 15, 2001, abstract) teach that MMP3, and MMP10, corresponding to stromelysins 1 and 2, share 82% sequence homology but exhibit difference in cellular synthesis and inducibility by cytokines and growth factors in vitro (see abstract). Further, Kerkela et al (British Journal of Cancer, vol. 84, 2001, abstract) teaches that while expression of stromelysin 1 (MMP 3) has been shown to correlate with tumor invasiveness in skin tumors, but that stromelysin 2 (MMP 10) expression did not. Therefore, the art does not support a predictable correlation between the structure of stromelysins and their functions. Further, with regard to SEQ ID NO 3 which encodes a protein lacking a key domain that is conserved among MMPs, and SEQ ID NO 1, which encodes only a fragment of a putative MMP, neither the specification nor the art teach a function for such, and therefore, the skilled artisan would be unable to determine whether a nucleic acid sequence belonged to the claimed genus of nucleic acids, other than by SEQ ID NO.

The specification further does not enable a use for the claimed sequences. The specification asserts that nucleic acids of SEQ ID NOS 1, 3, and 5 can be used to express proteins or make probes and primers to detect SEQ ID NOS 1, 3, and 5, however these are non specific uses that would be applicable to any nucleic acid sequence, and does not set forth a specific use for the claimed nucleic acids. The specification further asserts that SEQ ID NOS 1, 3, and 5 could be used to encode proteins wherein inhibition of such would be used to reduce hair growth (see p. 9). The specification cites Styczynski et al (US Patent 5,962,466) as teaching a method of inhibiting hair growth by inhibiting matrix metalloproteases. However, Styczynski et al only teach inhibiting MMP2 and MMP 9 collagenase activity, whereas MMP 2 and MMP 9 only showed 31.6 and 23.2% identity to the protein encoded by SEQ ID NO 5, which is far less

than the % identity that the protein encoded by SEQ ID NO 5 exhibited with stromelysins. Given the teachings of the art as set forth above, that is that matrix metalloproteases, while containing similar domains, have different activities, the skilled artisan would not be able to predictably correlate that inhibition of the polypeptide encoded by SEQ ID NO 5 would result in reducing hair growth based solely on the degree of % identity exhibited by the protein to various other MMPs.

To practice the invention as broadly as it is claimed, the skilled artisan would be required to first determine the substrate specificity and biological activity and function for the polypeptide of SEQ ID NO 5 and then determine if any of the polypeptides encoded by SEQ ID NOS 1 or 3 possessed the same. The skilled artisan would then be required to mutate every position to determine which amino acids could be changed but still result in a polypeptide with the same function. As neither the specification nor the art teach a function for the polypeptide encoded by SEQ ID NO 5, let alone that for SEQ ID NOS 1 and 3, the skilled artisan would be required to perform a large amount of trial and error anlysis, the results of which are unpredictable given the lack of guidance in the specification and the teachings of unpredictability in the art, to practice the invention as broadly as it is claimed. Such experimentation is considered undue.

Written Description

4. Claims 1, and 3-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to nucleic acids that consist essentially of (considered open terminology and interpreted like "comprising") a nucleotide sequence "according to SEQ ID NOS 1, 3, and 5", sequences having at least 85% identity to the nucleotide sequence according to SEQ ID NOS 1, 3, and 5, complements of SEQ ID NOS 1, 3, and 5, and sequences that hybridize to a sequence according to SEQ ID NOS 1, 3, and 5. Such recitation encompasses an extremely large genus of mutants, variants, and homologs of SEQ ID NOS 1, 3, and 5, from any source. Further, given that SEQ ID NO 1 does not encode a full length open reading frame, such claims further encompass genomic sequences that have not been taught or described by the specification.

The specification teaches that SEQ ID NO 5 encodes a matrix metalloprotease that has the highest % identity to the stromelysin family of matrix metalloproteases (46%). The specification teaches that SEQ ID NO 3 encodes a splice variant of SEQ ID NO 5,which lacks a Zn binding domain. The specification teaches that SEQ ID NO 1 encodes a fragment of SEQ ID NO 5, and SEQ ID NO 3. The specification teaches that the claims encompass variants that retain structural and functional characteristics more similar to MMP 25 (polypeptide encoded by SEQ ID NO 5) than to non type MMP 25 polypeptides. However, the specification does not teach the specific biological activity or function of SEQ ID NOS 3 or 5, such that the skilled artisan could determine whether a nucleic acid encoded a polypeptide belonging to such a large genus of polypeptides based solely on it's nucleic acid sequence or it's ability to hybridize to any of SEQ ID NO 1, 3, or 5.

While SEQ ID NO 5 appears to belong to the family of Matrix Metalloproteases, Matrix Metalloproteases comprise a large group of proteins that are involved in the degradation of the

extracellular matrix (see Yang and Kurkinen, J. BC, 1998; vol. 273, p 17893, col 1). This large group of proteins share similar domains with distinct structure and function, and have wide and often overlapping substrate specificities depending on the group they are in. These groups include collagenases, gelatinases, stromelysins, and membrane-type MMPs. However, this large group of proteins have different biological functions. Nagase teaches (Nagase and Woessner, J. BC, vol. 274, pp 21491-21494; 1999) that MMPs participate in many normal biological processes such as embryonic development, organ morphogenesis, nerve growth, apoptosis, etc (see p. 21493, col. 1 "Biological and Pathological Roles of Matrixins"). Nagase teaches that while the main function of matrixins is removal of the extracellular matrix during tissue resorption and progression of many diseases, MMPs also alter biological functions of extracellular matrix macromolecules by specific proteolysis. Nagase teaches that MMP-2 cleaves the Ala586-Leu587 bond in laminin and induces the migration of normal breast epithelial cells. In contrast, cleavage of type I collagen by MMP-1 and MMP-13 initiates keratinocyte migration during reepithelialization and osteoclast activation. Fig 1 of Nagase illustrates the structural similarities and differences between known matrix metalloproteases. Further, the degree of % identity of SEQ ID NO 5 to stromelysins does not indicate a particular biological function or activity for SEQ ID NOS 1, 3, or 5, or functional fragments of such, as the art teaches that stromelysins do not necessarily have the same activity. For example, Luo et al (JBC, vol. 277, pp 25527-25536, 2002) teaches that unlike most MMPs, ST3 (MMP 11) is characterized by a distinct substrate specificity and a specific regulation and is not directly involved in extracellular matrix degradation (see abstract). Bodey et al (In Vivo, vol. 15, 2001, abstract) teach that MMP3, and MMP10, corresponding to stromelysins 1 and 2, share 82% sequence

homology but exhibit difference in cellular synthesis and inducibility by cytokines and growth factors in vitro (see abstract). Further, Kerkela et al (British Journal of Cancer, vol. 84, 2001, abstract) teaches that while expression of stromelysin 1 (MMP 3) has been shown to correlate with tumor invasiveness in skin tumors, but that stromelysin 2 (MMP 10) expression did not. Therefore, the art does not support a predictable correlation between the structure of stromelysins and their functions. Further, with regard to SEQ ID NO 3 which encodes a protein lacking a key domain that is conserved among MMPs, and SEQ ID NO 1, which encodes only a fragment of a putative MMP, neither the specification nor the art teach a function for such, and therefore, the skilled artisan would be unable to determine whether a nucleic acid sequence belonged to the claimed genus of nucleic acids, other than by SEQ ID NO.

The claim encompass an extremely large genus of nucleic acids, such that the recitation of SEQ ID NO 3 or 5, or the partial fragment of SEQ ID NO 1 does not provide a teaching of a substantial portion of the claimed genus of mutants, variants, or homologs, or genomic sequences corresponding to such, from any source. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NOS: 1, 3, and 5 , the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more

than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for

patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1, and 3-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Robison (US Patent 6,331,427).

Robison teaches a sequence (SEQ IDNO 78), which is 99.4 % identical to the complement of SEQ ID NO 1, 90.2% identical to the complement of SEQ ID NO 3, and 99.2% identical to the complement of SEQ ID NO 5. Robison therefore teaches complements of SEQ ID NOS 1, 3, and 5, as well as sequences that would be capable of hybridizing to SEQ ID NOS 1, 3, and 5, under conditions of either normal or high stringency. Further, in teaching SEQ ID NO 78, Robison inherently sets forth the complete complement of SEQ ID NO 78, wherein the complete complement of SEQ ID NO 78 of Robison meets the limitation of claim 1b. Robison teaches PCR and hybridization reactions using the sequences taught by Robison (col. 16 and 17). Robison also teaches vectors and host cells comprising the polynucleotides taught by Robison (col. 45).

7. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Accession number AA424347 (Oct. 1997).

Accession number AA424347 teaches a sequence which is identical to positions 1-411 of SEQ ID NO 1, positions 653-1063 of SEQ ID NO 3, and positions 741-1151 of SEQ ID NO 5 (limitations of claim 1b as the claim is not limited to sequences that are 85% identical over the full length of the recited SEQ ID NOS).

Further, the sequence of the complete complement of Accession number AA424347 is inherently set forth in the teachings of the sequence, wherein the complement meets the

limitations of claim 1c and further would hybridize to the recited SEQ ID NOS under conditions of normal or high stringency.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 3-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Accession number AA424347 in view of Robison.

Accession number AA424347 teaches a sequence which is identical to positions 1-411 of SEQ ID NO 1, positions 653-1063 of SEQ ID NO 3, and positions 741-1151 of SEQ ID NO 5. AA424347 does not teach method of hybridization using such sequence or vectors or host cells comprising such, however Robison generally teaches PCR and hybridization reactions using nucleic acids (cols 16 and 17) and also teaches vectors and host cells comprising nucleic acids (col. 45). Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the protein encoded by the accession number for the purpose of analyzing it's function using the vectors and host cells and techniques taught by Robison and further to use hybridization to identify nucleic acids corresponding to the accession number to further characterize such, as taught by Robison.

Conclusion

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703) 308-6565. The examiner can normally be reached Monday-Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jehanne Souaya
Patent examiner
Art Unit 1634
Jehanne Souaya
5/27/03